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Date: September 23, 2004 **Total pages:** 15 (including cover sheet)

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Our Docket No. CMCC 654 DIV (2)
Your Docket No. **Client/Matter No.** 078856-00059

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MESSAGE:

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant: Bruce A. Yankner and Philip Nadeau

Serial No.: 10/086,398 Art Unit: 1617

Filed: February 28, 2002 Examiner: Theodore J. Criares

For: *METHODS FOR DECREASING BETA AMYLOID PROTEIN*

PTO/SB/17 (10-03)
Approved for use through 07/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

FEE TRANSMITTAL for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 330

Complete if Known	
Application Number	10/086,398
Filing Date	February 28, 2002
First Named Inventor	Bruce A. Yankner
Examiner Name	Theodore J. Criares
Art Unit	1617
Attorney Docket No.	CMCC 654 DIV (2)

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1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($) 0

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

			Extra Claims		Fee from below		Fee Paid
Total Claims	7	-20** =	0	X		=	
Independent Claims	1	-3** =	0	X		=	
Multiple Dependent						=	

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 0.00

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	330
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) _____

*Reduced by Basic Filing Fee Paid SUBTOTAL (3) ($) 330

SUBMITTED BY (Complete (if applicable))					
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PTO/SB/21 (08-03)
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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	10/086,398
Filing Date	February 28, 2002
First Named Inventor	Bruce A. Yankner
Art Unit	1617
Examiner Name	Theodore J. Criares
Total Number of Pages in This Submission: 14	Attorney Docket Number: CMCC 654 DIV (2)

ENCLOSURES *(Check all that apply)*

- [x] Fee Transmittal Form
  - [ ] Fee Attached
- [ ] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Response to Missing Parts/ Incomplete Application
  - [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
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- [ ] Petition to Convert to a Provisional Application
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- [ ] After Allowance communication to Group
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- [ ] Proprietary Information
- [ ] Status Letter
- [ ] Other Enclosure(s) (please identify below):

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual name	Rivka D. Monheit, Esq., Reg. No. 48,731 Pabst Patent Group LLP 400 Colony Square, Suite 1200, Atlanta, GA 30361
Signature	Rivka D. Monheit
Date	September 23, 2004

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Typed or printed name	Rivka D. Monheit		
Signature	Rivka D. Monheit	Date	September 23, 2004

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant: Bruce A. Yankner and Philip Nadeau

Serial No.: 10/086,398 Art Unit: 1617

Filed: February 28, 2002 Examiner: Theodore J. Criares

For: *METHODS FOR DECREASING BETA AMYLOID PROTEIN*

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 23-29 in the Office Action mailed February 24, 2004, in the above-identified patent application. A Notice of Appeal was filed on July 23, 2004. The Commissioner is hereby authorized to charge $330.00, the fee for the filing of this Appeal Brief for a large entity, to Deposit Account No. 50-3129. It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129.

(1) REAL PARTY IN INTEREST

The real parties in interest of this application are the assignee Children's Medical Center Corporation, Boston, MA, and the licensee Andrx Corporation, Davie, FL.

(2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

(3) STATUS OF CLAIMS ON APPEAL

Claims 23-29 are pending and on appeal. Claims 1-22 have been cancelled.

(4) STATUS OF AMENDMENTS

The claims were last amended in the amendment submitted via facsimile on September 11, 2003. An appendix sets forth the claims on appeal.

(5) SUMMARY OF THE INVENTION

The claimed invention is a composition for decreasing the production of Aβ comprising an effective amount of a compound decreasing blood cholesterol levels to decrease Aβ production by neuronal cells in an individual at risk of developing Alzheimers. (page 2, summary of the invention). Suitable cholesterol lowering compounds include HMG CoA reductase inhibitors such as the statins (page 6, lines 13-15); compounds which decrease uptake of dietary cholesterol such as bile acid binding resins and fibrates (page 6, lines 19-21); inhibitors of cholesterol biosynthetic enzymes (page 6, lines 16-18); and other cholesterol lowering compounds such as probucol, nicotinic acid, garlic and garlic derivatives and psyllium

(page 6, lines 21-23). Treatment is based on adminstration of one or more compositions effective to lower cholesterol blood levels at least 10%, which is believed to be sufficient to decrease production of Aβ. (page 3, summary of the invention).

(6) ISSUES ON APPEAL

The issues presented on appeal are:

(i) whether claims 23-29 are novel as required by 35 U.S.C. § 102(a) over U.S. Patent No. 4,866,090 to Hoffman *et al.* (" Hoffman"); U.S. Patent No. 5,350,758 to Wannamaker *et al.* ("Wannamaker"); and U.S. Patent No. 5,362,732 to Spielvogel *et al.* ("Spielvogel").

(ii) whether claims 26 and 27 are non-obvious as required by 35 U.S.C. § 103(a) over U.S. Patent No. 5,350,758 to Wannamaker *et al.* ("Wannamaker").

(7) ARGUMENTS

(a) The Claimed Invention

Appellants have demonstrated that elevated levels of cholesterol are correlated with elevated Aβ levels in the brain. Example 1 demonstrates that cholesterol actually increases the level of Aβ in human neuronal cultures. Example 2 shows that dietary cholesterol increases Aβ levels in the brain. Example 3 shows that HMG CoA reductase inhibitors inhibit the production of Aβ by human neurons. These results demonstrate that human neurons treated with either lovastatin, simvastatin, compactin, fluvastatin or pravastatin have significantly decreased levels of Aβ relative to controls. Subsequent studies with humans have confirmed the association between elevated cholesterol levels and Aβ levels in the brain

In the preferred embodiment, individuals with these risk factors are treated to lower blood cholesterol levels prior to developing any mental impairment attributable to AD, based on accepted neuropsychiatric and diagnostic criteria in clinical practice. Treatment is based on adminstration of one or more compositions effective to lower cholesterol blood levels at least 10%, which is believed to be sufficient to decrease production of Aβ.

The claimed invention is very specific: a composition for decreasing the production of Aβ comprising **an effective amount** of a compound decreasing blood cholesterol levels to decrease Aβ production by neuronal cells in an individual at risk of developing Alzheimers. The amount required to achieve this benefit is less than the amount required to lower cholesterol in patients with elevated cholesterol. This is advantageous because the amount of active is less, decreasing cost and side effects, which are not insignificant with these drugs. More relevantly, it also distinguishes the prior art compositions, which are provided in amounts required to treat atherosclerosis.

(i) Rejections Under 35 U.S.C. § 102

The Legal Standard

For a rejection of claims to be properly founded under 35 U.S.C. §102, it must be established that a prior art reference discloses each and every element of the claims. *Hybritech Inc v Monoclonal Antibodies Inc*, 231 U.S.P.Q. 81 (Fed. Cir. 1986), *cert. denied*, 480 US 947 (1987); *Scripps Clinic & Research Found v Genentech Inc*, 18 U.S.P.Q.2d 1001 (Fed. Cir. 1991). The Federal Circuit held in *Scripps*, 18 U.S.P.Q.2d at 1010:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. . . *There must be no difference* between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. (Emphasis added)

A reference that fails to disclose even one limitation will not be found to anticipate, even if the missing limitation could be discoverable through further experimentation. As the Federal Circuit held in *Scripps, Id.*:

> [A] finding of anticipation requires that all aspects of the claimed invention were already described in a single reference: a finding that is not supportable if it is necessary to prove facts beyond those disclosed in the reference in order to meet the claim limitations. The role of extrinsic evidence is to educate the decision-maker to what the reference meant to persons of ordinary skill in the field of the invention, not to fill in the gaps in the reference.

For a prior art reference to anticipate a claim, it must enable a person skilled in the art to practice the invention. The Federal Circuit held that "a §102(b) reference must sufficiently describe the claimed invention to have placed the public in possession of it. . . [E]ven if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling." *Paperless Accounting Inc v Bay Area Rapid Transit Sys.*, 231 U.S.P.Q. 649, 653 (Fed. Cir. 1986) (citations omitted).

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described in a single prior art reference. *Verdegaal Bros. v. Union*

Oil of California, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). A 102 rejection over multiple references is proper when the extra references cited show that a characteristic not disclosed is inherent. To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 U.S.P.Q.2d 1746, 1749 (Fed. Cir. 1991).

The Prior Art

Claims 23-29 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 4,866,090 to Hoffman *et al.* ("Hoffman"); U.S. Patent No. 5,350,758 to Wannamaker *et al.* ("Wannamaker"); and U.S. Patent No. 5,362,732 to Spielvogel *et al.* ("Spielvogel").

Hoffman discloses analogs of lovastatin and related analogs which are useful alone or in combination with bile acid sequestrants as antihypercholesterolemic agents "for the treatment of arteriosclerosis, hyperlipidemia, familial hypercholesterolemia and like diseases in humans".

Wannamaker discloses pharmaceutical compositions which are inhibitors of cholesterol biosynthesis and are useful in lowering serum cholesterol levels in patients having chronically and significantly elevated cholesterol levels, particularly for treatment of atherosclerosis (background of the invention).

Spielvogel discloses a class of boronated compounds that have many different properties (anti-cancer, anti-inflammatory, analgesic, antiinfective) and which might also include activity in

lowering cholesterol. This is a hypothetical disclosure that provides such a broad range that it encompasses everything and enables nothing.

The Claimed Invention

The claims on appeal define a composition comprising an effective amount of a compound decreasing blood cholesterol levels **to decrease Aβ production by neuronal cells in an individual at risk of developing Alzheimers**. There is no teaching or suggestion in the prior art that the compounds disclosed have any effect on the production of Aβ protein in neuronal cells. The prior art fails to define this end point or what an effective dosage would be to achieve this endpoint.

Moreover, the dosages that are effective in lowering the amount of amyloid precursor protein to decrease production of Aβ are different from those versus lowering cholesterol to treat or prevent atherosclerosis are different. The appellants disclose that a 10% decrease in serum cholesterol levels is believed to be sufficient to decrease production of Aβ protein in neurons (page 3, lines 11-13). Such a decrease would not be clinically effective in treating hypercholesterolemia (see, for example, Spielvogel, Example 15).

(ii) Rejections Under 35 U.S.C. § 103

The Legal Standard

The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177 (C.C.P.A. 1967), *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). In rejecting a claim under 35 U.S.C. § 103, the Examiner must establish a *prima facie* case that:

(i) the prior art suggests the claimed invention; and (ii) the prior art indicates that the invention would have a reasonable likelihood of success. *In re Dow Chemical Company,* 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988).

The prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. *In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Lalu and Foulletier*, 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). The Court of Appeals for the Federal Circuit warned that "the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for showing of the teaching or motivation to combine prior art references." *In re Dembiczak* , 175 F.3d 994 at 999 (Fed. Cir. 1999). The "question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination. *WMS Gaming, Inc. v International Game Technology*, 184 F.3d 1339 at 1355 (Fed. Cir. 1999). "[T]he showing must be clear and particular." *In re Dembiczak*, 175 F.3d 994 at 999 (Fed. Cir. 1999). Although with the answer in hand, the "solution" now appears obvious, that is not the test. The references must themselves lead those in the art to what is claimed. The references here do not disclose the disorder to be treated, the

selection of the composition to be used, nor the amount of active agent required. The composition therefore cannot be obvious.

The Prior Art

Claims 26 and 27 were rejected as obvious under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,350,758 to Wannamaker *et al.* ("Wannamaker").

Claims 26 and 27 are dependent on claim 23 and are directed to compounds which inhibit uptake of dietary cholesterol and which block or decrease endogenous cholesterol production, respectively. Claim 23 is directed to a composition for decreasing the production of Aβ comprising an effective amount of a compound decreasing blood cholesterol levels to decrease Aβ production by neuronal cells in an individual at risk of developing Alzheimers.

Wannamaker describes pharmaceutical compositions which are useful as inhibitors of squalene epoxidase and/or oxidosqualene cyclase and as a result inhibit cholesterol biosynthesis (col. 1, lines 10-13). Wannamaker describes pharmaceutical compositions which are useful as inhibitors of squalene epoxidase and/or oxidosqualene cyclase and as a result inhibit cholesterol biosynthesis (col. 1, lines 10-13).

There is no teaching or suggestion that the compounds disclosed would have any effect on the production of Aβ in neuronal cells. Accordingly, one of ordinary skill in the art would not be motivated to make or use the compounds disclosed by Wannamaker in an effective amount to inhibit the production of Aβ protein in neuronal cells.

(8) SUMMARY AND CONCLUSION

The prior art does not suggest that lowering cholesterol would have any effect on Aβ production in neuronal cells. The dosages required to decrease production of Aβ protein is different from that required to treat atherosclerosis, even though the serum component, cholesterol, is the same. Since the dosage is different, the claims are novel.

The prior art does not disclose the use of cholesterol lowering agents to decrease production of Aβ protein and therefore does not lead one to the selections required for one of ordinary skill in the art to make and use the claimed composition.

For the foregoing reasons, Appellants submit that claims 23-29 are patentable.

Respectfully submitted,

Rivka D. Monheit

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Date: September 23, 2004

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Appendix: Claims On Appeal

23. (previously amended) A composition for decreasing the production of Aβ comprising an effective amount of a compound decreasing blood cholesterol levels to decrease Aβ production by neuronal cells in an individual at risk of developing Alzheimers.

24. (original) The composition of claim 23 comprising an HMG CoA reductase inhibitor.

25. (original) The composition of claim 24 wherein the inhibitor is selected from the group consisting of lovastatin, simvastatin, fluvastatin, pravastatin, atorvastatin, cerivastatin, and compactin.

26. (original) The composition of claim 23 comprising a compound which inhibits uptake of dietary cholesterol.

27. (original) The composition of claim 23 wherein the composition blocks or decreases endogenous cholesterol production.

28. (original) The composition of claim 27 wherein the composition comprises an inhibitor of the cholesterol biosynthetic enzymes selected from the group consisting of 2,3-oxidosqualene cyclase, squalene synthase, and 7-dehydrocholesterol reductase.

29. (original) The composition of claim 23 wherein the composition is selected from the group consisting of a fibrate, a bile acid binding resin, probucol, nicotinic acid, garlic or garlic derivative, and psyllium.

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